ORIGINAL ARTICLE

Is the use of narrow-spectrum antibiotics too narrow-minded in the treatment of severe infections?

G. Höffken

Universitätsklinikum Carl Gustavus Carus, Technische Universität Dresden, Germany

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INTRODUCTION

Severe bacterial infections, such as nosocomial pneumonia, peritonitis, sepsis, and infection in immunocompromised patients, represent a major clinical burden, since they are associated with high rates of mortality. For example, mortality rates of over 60% for peritonitis and approximately 30% for either nosocomial pneumonia or sepsis have been reported [1,2]. The rates of mortality in severe infections are unacceptably high and methods for reducing these are continually being sought by both investigators and clinicians. However, it is difficult to identify any one particular factor as being actually responsible for the mortality associated with hospital-acquired severe infections in patients with a comorbid disease. It may be that patients die because of the severe underlying disease or because of emergent complications, such as adverse drug reactions. Few clear data are available that indicate that the nosocomial infection is an independent cause of mortality in patients with an underlying comorbid condition, i.e. that the nosocomial infection *per se* is responsible for the mortality.

Fagon et al. [3] examined the mortality that may be attributable to ventilator-associated nosocomial pneumonia. Forty-eight ventilated patients with nosocomial pneumonia were compared with well-matched controls who had no evidence of pneumonia (patients were matched for age, date of admission, duration of ventilation and Simplified Acute Physiologic Score). The total mortality rate was 54% compared with 27% for controls. The mortality attributable to nosocomial pneumonia (i.e. the mortality rate for cases minus the mortality rate for controls) was 27%. In this situation, the outcome in a substantial minority of patients might be improved by optimizing antibiotic therapy to effectively treat the infection.

This review discusses the treatment of severe infections in hospitalized patients with underlying diseases and examines the influence of antibiotic therapy strategies on clinical outcome by using studies in nosocomial pneumonia as examples.

Corresponding author and reprint requests: Professor G. Höffken, Universitätsklinikum Carl Gustavus Carus, Medizinische Klinik I/ Pneumologie, Fetcherstrasse 74, D-01307 Dresden, Germany
Tel.: +49 351458 3417
Fax: +49 351458 5765
E-mail: gert.hoeffken@mailbox.tu-dresden.de

CAUSATIVE ORGANISMS

A wide range of bacterial pathogens may be encountered in severe infections in hospitalized patients. For example, out of 8625 clinical isolates of bacteria from patients in an intensive care unit (ICU) or a hematology/oncology unit, the organisms most frequently isolated were staphylococci, enterococci, *Escherichia coli*, *Klebsiella* spp., *Enterobacter* spp., and *Pseudomonas aeruginosa* [4].

Resistance to antibiotic agents is a problem in a number of key bacterial pathogens. In *Enterobacter* and *Serratia* spp., the hyperproduction of β-lactamases by some strains confers resistance to a number of β-lactam antibiotics, such as the penicillins and cephalosporins [5]. Also, some Enterobacteriaceae, in particular *Klebsiella pneumoniae*, produce extended-spectrum β-lactamases that confer resistance to β-lactam antibiotics, including third-generation cephalosporins [6,7]. In addition, strains of methicillin-resistant *Staphylococcus aureus* (MRSA) are usually only susceptible to a limited number of antibiotic agents in current clinical use and concerns about this cannot be over-emphasized [8–10].

Usually when considering initial antibiotic therapy in severe infections, treatment must begin before the pathogens are identified. Therefore, therapy must be empirical and can be modified later according to the characterized pathogen.

Choice of empirical treatment should take into account the type of infection, the patient's age, the underlying disease (e.g. immunosupression, neutropenia), and any prior medical interventions, including previous antimicrobial therapy.

More severe infections are more difficult to treat empirically, since the spectrum of potential pathogens is wider

and the infection may also be polymicrobial. In addition, patients with more severe infections generally have been in hospital for longer and the greater the duration of hospitalization, the more likely it is that the causative bacteria will have reduced susceptibility to commonly prescribed antibiotics.

INFLUENCE OF ANTIBIOTIC THERAPY ON OUTCOME

Unlike other factors that may contribute to mortality (such as the presence of complications or the severity of the underlying disease), which are not amenable to interventions, the choice of initial empirical antibiotic therapy can be optimized so that the risk of mortality may be reduced. To do this, it is important to understand the reasons for treatment failure and the extent of the risk of using inadequate therapy.

A prospective study in patients with ICU-acquired pneumonia examined the reasons for changing initial empirical antibiotic therapy [11]. Out of 565 episodes of hospital-acquired pneumonia, 490 were treated with empirical therapy. Therapy consisted of a combination of two antibiotics in the majority (62%) of cases (e.g. a third-generation cephalosporin plus an aminoglycoside), monotherapy in 28% of cases (e.g. ciprofloxacin, imipenem/cilastatin, or cefotaxime) and treatment with three antibiotics in just 10% of cases (e.g. vancomycin plus two other antibiotics). Treatment was modified in 214 of 490 (44%) episodes. In 35 cases two reasons for changing therapy were given. The most common reason for treatment change was because the isolated organism was not susceptible to the administered antibiotics (i.e. the organism was not covered by the initial empirical therapy) (Figure 1). Other reasons included poor clinical response and development of resistance during therapy. When categorizing cases by the type of treatment regimen, the more narrow-spectrum regimen of two antibiotics was more frequently modified than the broad-spectrum, three-agent regimen because the organism was not covered by the initial empirical therapy (Figure 2).

Furthermore, in this study attributable mortality was significantly lower in patients who received appropriate initial therapy (i.e. at least one effective antibiotic had been prescribed) compared with those who received inappropriate therapy (16% vs. 25%; $P < 0.05$).

In another prospective study, 130 patients with suspected ventilator-associated pneumonia underwent mini-bronchoalveolar lavage (BAL), which was used to culture and characterize the causative pathogens [12]. Sixty patients had at least one potentially causative pathogen identified. Of these, 44 patients had received inappropriate antibiotic therapy, either because the bacterial isolate was resistant to the antibiotics prescribed or because the pathogen was not a bacterium (in just five cases). The most common reason to change therapy in these patients was a Gram-negative organism resistant to a third-generation cephalosporin (23), followed by MRSA requiring the addition of vancomycin (seven), and a Gram-negative organism resistant to an aminoglycoside (four), ciprofloxacin (three), or imipenem (two).

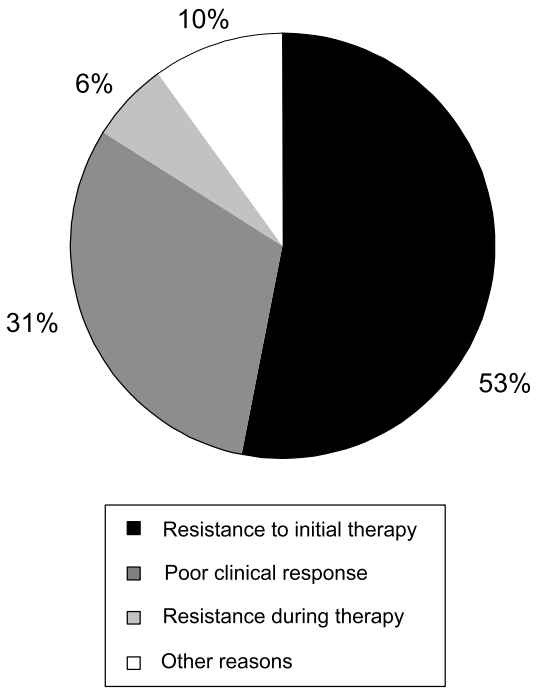

Fig 1 Reasons for modifying empirical therapy in episodes of ICU-acquired pneumonia (data from [11]). A total of 249 reasons were given for 214 episodes.

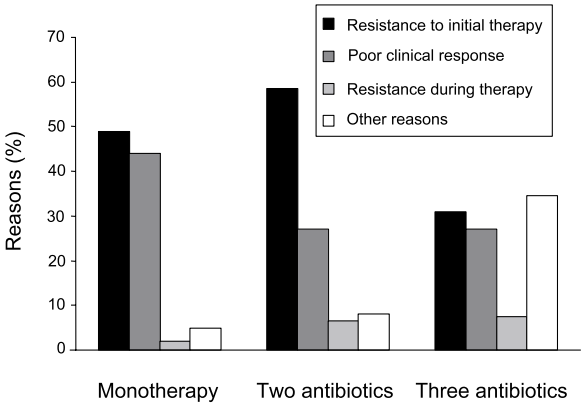

Fig 2 Reasons for modifying empirical therapy in episodes of ICU-acquired pneumonia by the treatment regimen administered (data from [11]). Monotherapy, 59 reasons were given for 50 episodes; two antibiotics, 164 reasons were given for 139 episodes; three antibiotics, 26 reasons were given for 25 episodes.

In the same study, patients who had their initial empirical therapy changed or needed to have antibiotic treatment started following the mini-BAL results had a significantly higher mortality rate than patients who did not require a change of therapy (61% vs. 33%; $P = 0.005$) (Figure 3). Thus, the initial choice of antibiotic therapy appears to have a considerable impact on mortality.

NARROW- VS. BROAD-SPECTRUM EMPIRICAL THERAPY

Initial empirical treatment with a narrow-spectrum regimen may subsequently need to be modified if indicated by the patient's clinical course or microbiological test results. An alternative would be to begin with a broad-spectrum regimen and de-escalate according to the clinical course and microbiological findings. The narrow-spectrum strategy relies on having sufficient time available to modify a failing therapy before the patient's clinical condition deteriorates. This may be the case in nonsevere infections, but severe infections are more complex so this approach may not be suitable. Furthermore, inappropriate use of narrow-spectrum antibiotics is likely to contribute to increased drug resistance.

The need for early and effective antibiotic treatment was examined in a prospective study of 132 patients hospitalized for longer than 72 h and who had suspected ventilator-associated pneumonia [13]. BAL was used to confirm the diagnosis of pneumonia and to characterize the causative pathogens. Of the 65 episodes (in 62 patients) that satisfied the microbiologic definition of ventilator-associated pneumonia, 50 had been treated with antibiotics prior to BAL. The mortality rate was significantly lower in patients whose initial (prelavage) antibiotic regimen was adequate (as defined by the subsequent lavage results) than in patients whose antibiotic regimen was inadequate (38% vs. 91%; $P < 0.001$) (Figure 3). Altering treatment when the pathogens were identified after lavage (after approximately 24 h) resulted in more patients receiving appropriate antibiotic therapy; however, the mortality rate did not improve compared with patients receiving inappropriate therapy. This indicates that severe infections progress rapidly and so there may not be time to successfully change antibiotic therapy if the initial empirical treatment fails. Therefore, the prompt use of an adequate broad-spectrum empirical therapy is beneficial.

This strategy is confirmed by an earlier study (conducted in 1985–87) of 67 patients hospitalized due to severe community-acquired pneumonia [14]. The majority of patients received a broad-spectrum therapy of erythromycin plus tobramycin or cefamandole and the mortality rate in these patients was just 15%. This was compared with 32% in patients who initially received narrow-spectrum therapy. In addition, it was necessary to modify treatment because of poor response in fewer patients receiving the broad-spectrum therapy than in patients receiving another treatment regimen.

CHOICE OF BROAD-SPECTRUM ANTIBIOTIC AGENTS

In the USA, Thornsberry and Yee [15] reported on the comparative activities of antibiotic agents from different classes against over 12 000 clinical isolates. Overall, the carbapenem, imipenem, the fluoroquinolone, ciprofloxacin, and the 'fourth-generation' cephalosporin, cefepime, were the most active antibiotics tested, since over 80% of strains tested were susceptible to these agents (Figure 4).

Recommendations and guidelines have been issued by several societies and organizations concerning the treatment of severe infections, e.g. nosocomial pneumonia [16]. The American Thoracic Society [1] recommends broad-spectrum antibiotic therapy for initial empirical treatment of severe nosocomial pneumonia, using imipenem plus ciprofloxacin or an aminoglycoside, piperacillin, ceftazidime, β-lactam plus β-lactamase inhibitor, or aztreonam.

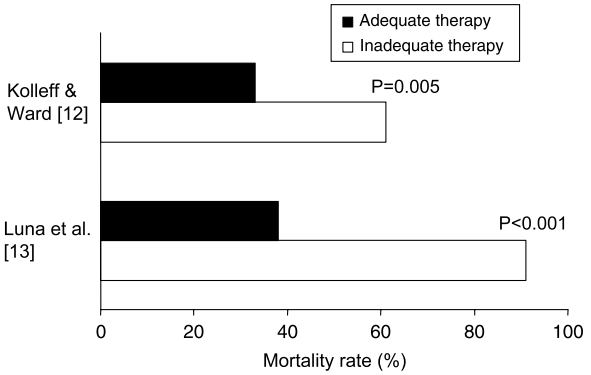

Fig 3 Mortality rates in patients with ventilator-acquired pneumonia when treated initially with adequate or inadequate therapy (data from [12] and [13]).

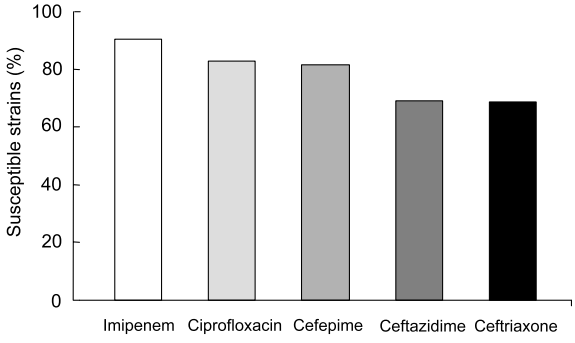

Fig 4 Proportion of clinical bacterial isolates ($n > 12\,000$) susceptible to a selection of antibiotic agents in current clinical use (data from [15]).

Also, when selecting antibiotics for broad-spectrum therapy, it is important to consider local as well as national resistance patterns.

CONCLUSION

In severe infections, treatment must be both prompt and appropriate in order to reduce the infection-associated mortality. The use of appropriate, broad-spectrum antibiotic regimens in nosocomial and ventilator-acquired pneumonia has been associated with better outcomes than inappropriate therapies. Thus, the use of broad-spectrum antibiotic therapy as initial empirical treatment in severe infections is recommended. The initial regimen may subsequently be modified or de-escalated as appropriate when results from microbiologic tests become available.

REFERENCES

1. American Thoracic Society. Hospital-acquired pneumonia in adults: diagnosis, assessment of severity, initial antimicrobial therapy, and preventive strategies. A consensus statement, American Thoracic Society, November 1995. *Am J Respir Crit Care Med* 1996; **153**: 1711–25.
2. Friedman G, Silva E, Vincent JL. Has the mortality of septic shock changed with time? *Crit Care Med* 1998; **26**: 2078–86.
3. Fagon JY, Chastre J, Hance AJ, Montravers P, Novara A, Gibert C. Nosocomial pneumonia in ventilated patients: a cohort study evaluating attributable mortality and hospital stay. *Am J Med* 1993; **94**: 281–8.
4. Verbist L. Epidemiology and sensitivity of 8625 ICU and hematology/oncology bacterial isolates in Europe. International Study Group. *Scand J Infect Dis Suppl* 1993; **91**: 14–24.
5. Livermore DM. β-lactamase-mediated resistance and opportunities for its control. *J Antimicrob Chemother* 1998; **41** (Suppl. D): 25–41.
6. Livermore DM, Yuan M. Antibiotic resistance and production of extended-spectrum β-lactamases amongst *Klebsiella* spp. from intensive care units in Europe. *J Antimicrob Chemother* 1996; **38**: 409–24.
7. Rahal J. Extended-spectrum beta-lactamases: how big is the problem? *Clin Microbiol Infect* 2000; **6** (Suppl. 2): 2–6.
8. Maranan MC, Moreira B, Boyle-Vavra S, Daum RS. Antimicrobial resistance in staphylococci. Epidemiology, molecular mechanisms, and clinical relevance. *Infect Dis Clin North Am* 1997; **11**: 813–49.
9. Péchère JC. Current and future management of infections due to methicillin-resistant staphylococci infections: the role of quinupristin/dalfopristin. *J Antimicrob Chemother* 1999; **44** (Topic A): 11–18.
10. Carbon C. MRSA and MRSE: is there an answer? *Clin Microbiol Infect* 2000; **6** (Suppl. 2): 17–22.
11. Alvarez-Lerma F. Modification of empiric antibiotic treatment in patients with pneumonia acquired in the intensive care unit. ICU-Acquired Pneumonia Study Group. *Intensive Care Med* 1996; **22**: 387–94.
12. Kollef MH, Ward S. The influence of mini-BAL cultures on patient outcomes: implications for the antibiotic management of ventilator-associated pneumonia. *Chest* 1998; **113**: 412–20.
13. Luna CM, Vujacich P, Niederman MS et al. Impact of BAL data on the therapy and outcome of ventilator-associated pneumonia. *Chest* 1997; **111**: 676–85.
14. Pachon J, Prados MD, Capote F, Cuello JA, Garnacho J, Verano A. Severe community-acquired pneumonia. Etiology, prognosis, and treatment. *Am Rev Respir Dis* 1990; **142**: 369–73.
15. Thornsberry C, Yee YC. Comparative activity of eight antimicrobial agents against clinical bacterial isolates from the United States, measured by two methods. *Am J Med* 1996; **24** (100): 26S–38S.
16. Mandell LA, Campbell GD Jr. Nosocomial pneumonia guidelines: an international perspective. *Chest* 1998; **113** (Suppl. 3): 188S–93S.